IN THE UNITED STATES PATENT & TRADEMARK OFFICE

APPLICANT: R. BOISSONNEAULT
EXAMINER: J. LIPOVSKY
SERIAL NO: 07/061,646
ART UNIT: 125
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PAPER NO:
FOR: GRADUATED ESTROGEN CONTRACEPTIVE

DECLARATION UNDER RULE 132

Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

Dear Sir:

I, Leon Speroff, a citizen of the United States of America, residing at 13569 County Line Road, Chagrin Falls, Ohio 44022, hereby declare:

1. I am professor at the Department of Reproductive Biology, Case Western Reserve University, School of Medicine, Cleveland, Ohio. I am a board certified Diplomate of the American Board of Obstetrics and Gynecology and have a subspeciality certification in the division of Reproductive Endocrinology. I attach with this declaration and marked as Exhibit A my full Curriculum Vitae which outlines my education, professional training, fellowships, academic appointments, hospital appointments, memberships in professional organizations, activities, and publications.

2. I am familiar with the Application for United States Letters Patent for "Graduated Estrogen Contraceptive", United States Serial Number 061,646.

3. I am also familiar with an article appearing in Volume 35, No. 6 of CONTRACEPTION published in June of 1987 entitled "A Comparison of A New Graduated Estrogen Formulation with Three Constant-Dosed Oral Contraceptives". This is a summary article reporting on a multicenter clinical trial of a new graduated estrogen formulation with three constant-dosed combination oral contraceptives. The new graduated estrogen formulation consisted of five tablets containing 20 micrograms of ethinyl estradiol and 1.0 milligrams of norethindrone acetate each, seven tablets containing 30 micrograms of ethinyl estradiol and 1.5 milligrams norethindrone acetate each and the last

1.0 mg norethindrone acetate each tablet, Loestrin 1.5/30, constant dose of 30 µg ethinyl estradiol and 1.5 mg norethindrone acetate each tablet, and Norlestrin 1/50, constant dose 50 µg ethinyl estradiol and 1.0 mg norethindrone acetate each tablet.

4. As a Consultant for Warner-Lambert in their oral contraceptive program, I had access to and have studied the data from the multicenter study. The graduated estrogen product, Estrostep, demonstrated a statistically significant improvement in cycle control compared to the constant dosed 1/20 product and control equivalent to the medium dosed 1/50 product. Unlike any phasic oral contraceptive (OC), Estrostep exhibited overall cycle control superior to an existing low dose of OC and parity with a higher dosed product (a dose now considered unacceptable). Therefore these results demonstrated a product with less breakthrough bleeding.

The effect of graduated estrogen can be more clearly demonstrated when the incidence of breakthrough bleeding is examined on a weekly basis (Table I data are not published in the CONTRACEPTION article but are attached to this declaration and marked as Exhibit B). It is obvious from these data that in the first week of the cycle the rate of breakthrough bleeding is minimal despite the low absolute dose of estrogen employed. However as the endometrium develops, the incidence of bleeding increases. It is apparent that 20 µg of estrogen can be used early within the contraceptive cycle without compromising cycle control. It is also evident that, through the use of graduated estrogen, Estrostep sustains control in the second and third week of the cycle equal to or better than the constant dosed 30 and 50 µg product.

The safety implications of reducing total estrogen exposure are most significant. Estrogen's potential impact on the clotting system is the number one safety concern. Graduated estrogen offers a dosing alternative that minimizes estrogen exposure while maintaining good cycle control.

5. In addition to the favorable impact on breakthrough bleeding, the graduated estrogen product, Estrostep, has a beneficial effect on the cholesterol-lipoprotein profile. Clinical studies indicate a statistically significant increase in HDL-cholesterol

reported that the greatest rise in mean HDL-C levels was observed with Estrostep (2.66 mg/dl) whereas only a statistically insignificant rise (0.98 mg/dl) was observed with Loestrin 1.5/30.

6. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the Application or any Patent issued thereon.

3/13/89
Date

Leon Speroff, M.D.

Attachments